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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,748	08/11/2006	Patrick Gerard Johnston	36290-0415-00-US	1280

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
09/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,748	JOHNSTON ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 29-52* is/are pending in the application.

4a) Of the above claim(s) *1-15,29,40,41,45 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-33,36-39,42-44 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Examiner and Art Unit handling this Application have changed. Please address further correspondence to Richard Schnizer, Art Unit 1635, whose contact information is given at the end of this Action.

Election/Restrictions

Applicant's election of Group III in the reply filed on 06/10/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has brought to the attention of the examiner that Claim 29 and dependent Claims 40 and 41 were inadvertently included in Group III. Claim 29 is directed to a composition comprising a c-FLIP inhibitor as a sole cytotoxic agent in the absence of a chemotherapeutic agent and therefore contains different reagents as the other Groups. The restriction requirement now stands as the following groups:

Claims 1 and 2

Claims 3-15, 45, and 46

Claims 29, 40 and 41

Claims 30-44, 47-52

Election of Group III is now considered Group IV.

Claims 1-15, 29, 40, 41, 45 and 46 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no

allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/10/2008.

After further consideration the species requirement for "chemotherapeutic agent" has been withdrawn.

Claims 34 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/10/2008.

Claims 30-33, 36-39, 42-44 and 47-52 will be examined on the merits.

Specification/Compliance with Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the following reason(s). Applicant's attention is directed to the final rule making notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998). **The specification at page 51, lines 18-21, discloses nucleotide sequences in excess of 9 bases that are not accompanied by a SEQ ID NO.** If these sequences are listed in the current Sequence Listing, then the specification should be amended to include the appropriate SEQ ID NO in each of the passages referred to above. If these

sequences are not in the current Sequence Listing, then in addition to amending the disclosure to include appropriate SEQ ID NOS, Applicant must also provide:

An substitute computer readable form (CRF) copy of the "Sequence Listing".

An substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

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For questions regarding compliance to these requirements, please contact:

- For Rules Interpretation, call (571) 272-0951
- For Patentin Software Program Help, call Patent EBC at 1-866-217-9197 or directly at 703-305-3028 / 703-308-6845 between the hours of 6 a.m. and 12 midnight, Monday through Friday, EST.
- Send e-mail correspondence for Patentin Software Program Help @ ebc@uspto.gov.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 30, 31, 34, 36-39, 42, 47, and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegmund et al (Molecular Medicine 8(11): 725–732, 2002, of record) and Xiang et al (Oncogene 21: 3611-3619, 2002).

Siegmund taught that tumor cell sensitivity to TRAIL-induced apoptosis could be enhanced by treatment with siRNA directed to c-FLIP.

Xiang taught that tumor cell sensitivity to TRAIL-induced apoptosis could be enhanced by treatment with CPT-11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the siRNA of Siegmund with the CPT-11 of Xiang in order to form a composition for the treatment of tumors. One would have been motivated to do so in order to obtain the art-recognized benefit of each component in enhancing TRAIL-induced apoptosis of tumor cells. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06(I).

Regarding claims 36 and 37, the ratio of c-FLIP siRNA and chemotherapeutic agent is considered to be a result effective variable that is routinely optimized by those of ordinary skill.

Regarding claims 38 and 39, absent evidence to the contrary, the extent to which p53 is inactivated and the precise identity of the p53 mutation have no effect on the nature of the claimed composition, and receive no patentable weight.

Regarding claims 42, 51, and 52, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the siRNA of Siegmund and the CPT-11 of Xiang into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Regarding claims 49-52 and the limitation requiring the absence of a death receptor binding member, it would have been obvious to formulate the composition or kit either with or without a death domain binding member (such as TRAIL). This is simply a matter of design choice. On the one hand, it would be simple and efficient to administer all three molecules (siRNA, CPT-11, and TRAIL) in one composition, thereby limiting the number of invasive administrations. On the other hand, one it would also be obvious to administer the siRNA and CPT-11 first in order to place the target tumor cells in a state in which they are maximally responsive to TRAIL when it is administered separately later.

Thus the invention as a whole was prima facie obvious.

Claims 43, 44, and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Siegmund et al (Molecular Medicine 8(11): 725–732, 2002) and Xiang et al (Oncogene 21: 3611-3619, 2002) as applied to claims 30, 31, 34, 36-39, 42, 47, and 49-52 above, and further in view of Tuschl et al(1) (US 20040259247) and Tuschl et al(2) (The siRNA User Guide. 4/16/03, 6 pages).

Siegmund and Xiang can be combined to render obvious a composition comprising CPT-11 and an siRNA directed against c-FLIP.

These references do not teach an siRNA comprising either SEQ ID NO: 1 or SEQ ID NO: 2.

Tuschl (1) provided extensive teaching on siRNAs their design, and their use in inhibiting a selected target gene. Tuschl taught that siRNA provides enhanced efficacy compared to prior art compounds (paragraph 8, for example). The entire document is directed to the design and use of siRNA.

Tuschl (2) taught that there were ample providers of siRNA in the art at the time of invention, and that there was also a publicly available computer program to find siRNAs for a given target. Tuschl (2) also provided ample guidance on the design of siRNA compounds.

Since the prior art taught the use of siRNA to inhibit c-FLIP, and since the prior art provides a wealth of information on the design of siRNAs, it would have been obvious to make any siRNA to c-FLIP. It is noted that the methods taught in the prior art may not predict with 100% accuracy which siRNA compounds will inhibit c-FLIP, however, with the use of the prior art algorithms, basic teachings, and siRNA vendors, it would have been routine to make an test any number of siRNA compounds targeted to MCL1, where the number of compounds in the genus is limited by the sequence of the MCL1 gene. The instant specification provides no evidence that the claimed siRNAs have some unexpected properties and further provides no evidence that the known methods of the prior art would not provide for an siRNA that comprises either SEQ ID

NO: 1 or SEQ ID NO: 2. The invention as a whole would therefore have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 30-34, 36-39, 42, 47, and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hyer et al. (Cancer Biology and Therapy, Vol. 1 (4), pp.401-406, 2001), Uslu et al. (Clin. Cancer Res., Vol. 3(6), pp.963-972, 1997), Ni et al. (US 20050244857) and Tuschl et al (US 7,056,704).

The claims are drawn to a composition comprising a c-FLIP inhibitor, a chemotherapeutic agent, the CH11 antibody, wherein the c-FLIP inhibitor is RNAi comprising either SEQ ID NO:1 or 2.

Hyer taught a method of killing DU145 prostate cancer cells comprising administration of a c-FLIP antisense oligonucleotide and CH11 antibody (see Fig. 5).

Uslu taught the treatment of DU145 prostate cancer cells with chemotherapeutic agents (CDDP, adriamycin and Etoposide) followed by anti-FAS CH-11 treatment resulted in synergistic cytotoxicity and apoptosis.

Ni taught several therapeutic agents that are useful for combination therapy treatment of cancer. These agents include, CDDP, 5-FU, CPT-11, and Cisplatin. See paragraphs 283, 333, 338-341, and 547.

Tuschl stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to prepare a composition comprising the c-FLIP antisense and CH11 antibody taught by Hyer, and a chemotherapeutic agent as taught by Uslu or Ni. One would have been motivated to do so in order to obtain the art-recognized benefit of each component in treating tumors. It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06(I). It would have been obvious to use any of the chemotherapeutic agents of Uslu or Hyer. MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case it was clearly recognized that CPT-11, f-FU, and cisplatin were all chemotherapeutic agents.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute siRNA for the antisense of Hyer. One would have been motivated to do so in order to take advantage of the increased efficacy noted by Tuschl.

Regarding claims 42, 51, and 52, it would have been obvious to one of ordinary skill in the art at the time of the invention to organize the siRNA of Tuschl/Hyer and the CPT-11 of Ni into a kit because one of skill in the art appreciates that organizing experimental reagents prior to use is standard laboratory practice which reduces the frequency of errors.

Regarding claims 49-52 and the limitation requiring the absence of a death receptor binding member, it would have been obvious to formulate the composition or kit either with or without a death domain binding member (such as CH-11). This is simply a matter of design choice. On the one hand, it would be simple and efficient to administer all three molecules (siRNA, CPT-11, and CH-11) in one composition, thereby limiting the number of invasive administrations. On the other hand, one it would also be obvious to administer the siRNA and CPT-11 first in order to place the target tumor cells in a state in which they are maximally responsive to death receptor stimulation by CH-11 when it is administered separately later.

Thus the invention as a whole was prima facie obvious.

Prior Art Made of Record but not Relied Upon

Wajant et al (US 20040126791) taught compositions and methods for treating TRAIL-resistant cancer cells including treatment with c-FLIP siRNAs, apoptosis inducing drugs, and chemotherapeutics. See abstract, paragraphs 12, 17, 18, 55-58, 64-66, and 72.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer, Ph. D./
Primary Examiner, Art Unit 1635